

WHAT IS CLAIMED IS:

1. A method of treating or preventing pain in a subject; said method comprising decreasing an intracellular chloride level in a central nervous system (CNS) neural cell of said subject.
2. The method of claim 1, wherein said method comprises modulating the activity or expression of a chloride transporter in said CNS cell, thereby to decrease said chloride level.
3. The method of claim 2, wherein said chloride transporter is KCC2.
4. The method of claim 3, said method further comprises increasing said KCC2 activity or expression.
5. The method of claim 1, wherein said CNS neural cell is a spinal cord neural cell.
6. The method of claim 1, wherein the signal of said pain originates in a peripheral nervous system (PNS) cell or sensory fiber transsynaptic to said CNS neural cell.
7. The method of claim 1, wherein said pain is neuropathic pain.
8. The method of claim 7, wherein said neuropathic pain is associated with a nerve or tract injury.
9. The method of claim 7, wherein said neuropathic pain is selected from the group consisting of somatic and visceral pain.
10. The method of claim 1, wherein said pain is selected from the group consisting of chronic inflammatory pain, pain associated with arthritis, fibromyalgia, back pain, cancer-associated pain, pain associated with digestive disease, pain associated with Crohn's disease, pain associated with autoimmune disease, pain associated with endocrine disease, pain associated with diabetic neuropathy, phantom limb pain,

spontaneous pain, chronic post-surgical pain, chronic temporomandibular pain, causalgia, post-herpetic neuralgia, AIDS-related pain, complex regional pain syndromes type I and II, trigeminal neuralgia, chronic back pain, pain associated

5 with spinal cord injury and recurrent acute pain.

11. The method of claim 1, wherein said method comprises administering to said subject a compound capable of decreasing said intracellular chloride level in said CNS cell.

10 12. The method of claim 11, wherein said compound is capable of modulating the activity or expression of a chloride transporter in said CNS cell.

13. The method of claim 12, wherein said chloride transporter is KCC2.

15 14. The method of claim 13, wherein said compound is capable of increasing said KCC2 activity or expression.

15. The method of claim 14, wherein said compound is an inhibitor of TrkB.

16. The method of claim 15, wherein said inhibitor is
20 selected from the group consisting of K-252a and an anti-TrkB antibody.

17. The method of claim 13, wherein said compound is an inhibitor of cyclic AMP-dependent kinase (PKA).

18. The method of claim 17, wherein said inhibitor is H-89.

25 19. The method of claim 13, wherein said compound is an inhibitor of calmodulin-dependant kinase (CAM kinase).

20. The method of claim 19, wherein said inhibitor is KN-93.

21. The method of claim 3, wherein said KCC2 comprises an amino acid sequence substantially identical to a sequence
30 selected from the group consisting of SEQ ID NO: 2, 4, 6 and a fragment thereof.

22. A composition for the treatment or the prevention of pain in a subject, said composition comprising:

- (a) a compound capable of decreasing an intracellular chloride level in a CNS neural cell; and
- (b) a pharmaceutically acceptable carrier.

23. The composition of claim 22, wherein said compound is capable of modulating the activity or expression of a chloride transporter in said CNS neural cell.

24. The composition of claim 23, wherein said chloride transporter is KCC2.

25. The composition of claim 24, wherein said compound is capable of increasing said KCC2 activity or expression.

26. A commercial package comprising the composition of claim 22 together with instructions for its use in the treatment or prevention of pain.

27. A commercial package comprising a compound capable of decreasing an intracellular chloride level in a CNS neural cell together with instructions for its use the treatment or prevention of pain.

28. The commercial package of claim 27, wherein said compound is capable of modulating the activity or expression of a chloride transporter in said CNS neural cell.

29. The commercial package of claim 28, wherein said chloride transporter is KCC2.

30. The commercial package of claim 29, wherein said compound is capable of increasing said KCC2 activity or expression.

31. Use of the composition of claim 22 for the treatment or prevention of pain.

32. Use of the composition of claim 22 for the preparation of a medicament for the treatment or prevention of pain.

33. Use of a compound capable of decreasing an intracellular chloride level in a CNS neural cell for the treatment or prevention of pain.

34. Use of a compound capable of decreasing an intracellular chloride level in a CNS neural cell for the preparation of a medicament for the treatment or prevention of pain.
35. The use of claim 33, wherein said compound is capable of modulating the activity or expression of a chloride transporter in said CNS cell.
- 5 36. The use of claim 35, wherein said chloride transporter is KCC2.
37. The use of claim 36, wherein said compound is capable of increasing said KCC2 activity or expression.
- 10 38. The use of claim 37, wherein said compound is an inhibitor of TrkB.
39. The use of claim 38, wherein said inhibitor is selected from the group consisting of K-252a and an anti-TrkB antibody.
- 15 40. The use of claim 37, wherein said compound is an inhibitor of cyclic AMP-dependent kinase (PKA).
41. The use of claim 40, wherein said inhibitor is H-89.
42. The use of claim 37, wherein said compound is an inhibitor of calmodulin-dependant kinase.
- 20 43. The use of claim 42, wherein said inhibitor is KN-93.
44. A method of identifying or characterizing a compound for treatment or prevention of pain, said method comprising:
 - (a) contacting a test compound with a CNS-derived cell; and
 - 25 (b) determining whether said intracellular chloride level is decreased in the presence of the test compound; wherein said decrease is an indication that said test compound may be used for treatment or prevention of pain.
45. A method of identifying or characterizing a compound for treatment or prevention of pain, said method comprising:
 - 30 (c) contacting a test compound with a CNS-derived cell expressing a chloride transporter; and

(d) determining whether activity or expression of said chloride transporter is modulated in the presence of the test compound in such a way that the level intracellular chloride is decreased;

5 wherein said modulation is an indication that said test compound may be used for treatment or prevention of pain.

46. The method of claim 45, wherein said chloride transporter is KCC2.

47. The method of claim 46, wherein said method comprises 10 determining whether said KCC2 expression or activity is increased in the presence of the test compound and said modulation is an increase.

48. The method of claim 47, wherein said KCC2 activity is determined by measuring a parameter selected from the group 15 consisting of potassium transport, chloride transport, intracellular chloride level and anion reversal potential.

49. The method of claim 44, wherein said pain is selected from the group consisting of chronic inflammatory pain, pain associated with arthritis, fibromyalgia, back pain, cancer-20 associated pain, pain associated with digestive disease, pain associated with Crohn's disease, pain associated with autoimmune disease, pain associated with endocrine disease, pain associated with diabetic neuropathy, phantom limb pain, spontaneous pain, chronic post-surgical pain, chronic 25 temporomandibular pain, causalgia, post-herpetic neuralgia, AIDS-related pain, complex regional pain syndromes type I and II, trigeminal neuralgia, chronic back pain, pain associated with spinal cord injury and recurrent acute pain.

50. A method of identifying or characterizing a compound for 30 treatment or prevention of pain, said method comprising:

(a) contacting a test compound with a CNS-derived cell comprising a first nucleic acid comprising a transcriptionally regulatory element normally associated with

a chloride transporter gene, operably linked to a second nucleic acid comprising a reporter gene capable of encoding a reporter protein; and

(b) determining whether reporter gene expression or

5 reporter protein activity is modulated in the presence of said test compound;

wherein said modulation in reporter gene expression or reporter protein activity being an indication that said test compound may be used for treatment or prevention of pain.

10 51. The method of claim 50, wherein said chloride transporter is KCC2.

52. The method of claim 51, wherein said reporter gene expression or reporter protein activity is increased in the presence of said test compound.

15 53. A method for decreasing nociception in a subject, said method comprising decreasing intracellular chloride in a CNS neural cell of said subject.

54. The method of claim 53, wherein said method comprises modulating chloride transporter activity or expression in 20 said CNS neural cell.

55. The method of claim 54, wherein said chloride transporter is KCC2.

56. The method of claim 55, said method further comprises increasing said KCC2 activity or expression.

25 57. The method of claim 55, wherein said method further comprises contacting said CNS neural cell with a compound capable of increasing KCC2 activity or expression.

58. The method of claim 57, wherein said compound is an inhibitor of TrkB.

30 59. The method of claim 58, wherein said inhibitor is selected from the group consisting of K-252a and an anti-TrkB antibody.

60. The method of claim 57, wherein said compound is an inhibitor of cyclic AMP-dependent kinase (PKA).

61. The method of claim 60, wherein said inhibitor is H-89.

62. The method of claim 57, wherein said compound is an inhibitor of calmodulin-dependant kinase.

63. The method of claim 62, wherein said inhibitor is KN-93.

64. The method of claim 55, wherein said KCC2 comprises an amino acid sequence substantially identical to a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6 and a fragment thereof.

65. A method for diagnosing or prognosticating pain associated with CNS dysfunction in a subject experiencing pain, said method comprising determining whether a test CNS intracellular chloride level is increased relative to a corresponding control chloride level; wherein said increase is an indication that said subject is experiencing pain associated with CNS dysfunction.

66. The method of claim 65, said method further comprises determining whether CNS chloride transporter activity or expression is modulated relative to a control transporter activity or expression.

67. The method of claim 66, wherein said chloride transporter is KCC2.

68. The method of claim 67, said method further comprises determining whether said KCC2 activity or expression is decreased relative to said control activity or expression.

69. The method of claim 65, wherein said control intracellular chloride level is selected from the group consisting of:

30 (a) an established standard;

(b) a corresponding intracellular chloride level determined in said subject at an earlier time;

(c) a corresponding intracellular chloride level determined in said subject when said subject is experiencing less pain or substantially no pain; and

5 (d) a corresponding intracellular chloride level determined in a control subject experiencing less pain or substantially no pain.

70. The method of claim 68, wherein said control activity or expression is selected from the group consisting of:

(a) an established standard of KCC2 activity or expression;

10 (b) a corresponding level of KCC2 activity or expression determined in said subject at an earlier time;

(c) a corresponding level of KCC2 activity or expression determined in said subject when said subject is experiencing less pain or substantially no pain; and

15 (d) a corresponding level of KCC2 activity or expression determined in a control subject experiencing less pain or substantially no pain.

71. The method of claim 67, wherein said KCC2 activity is determined by measuring a parameter selected from the group 20 consisting of potassium transport, chloride transport, intracellular chloride level and anion reversal potential.

72. The method of claim 65, wherein said intracellular chloride level is determined by:

(a) administering an indicator compound indicative of 25 intracellular chloride level to said subject such that it is contacted with a CNS neural cell of said subject;

(b) assessing an *in vivo* signal associated with said indicator compound.

73. The method of claim 65, wherein said pain associated with 30 CNS dysfunction is neuropathic pain.

74. The method of claim 73, wherein the indicator compound is a radionuclide.

75. The method of claim 75, wherein the radionuclide is selected from the group consisting of ^{201}Tl , ^{99}Tcm -tetrofosmin, ^{99}Tcm -MIBI, ^{99}Tcm -HMPAO and ^{36}Cl .

76. The method of claim 73, wherein said *in vivo* signal is 5 assessed by an imaging technique.

77. The method of claim 72, wherein said *in vivo* signal is the retention index of said indicator compound.

78. The method of claim 76, wherein the imaging technique is selected from the group consisting of single photon emission 10 computed tomography, positron emission tomography and magnetic resonance imaging.

79. The method of claim 73, wherein said indicator compound is indicative of KCC2 expression.

80. The method of claim 79, wherein said indicator compound 15 is an antibody directed against KCC2.

81. A method of treating pain associated with CNS dysfunction in a subject, said method comprising:

- (a) diagnosing or prognosticating, according to the method of claim 65, pain associated with CNS dysfunction in 20 said subject;
- (b) decreasing an intracellular chloride level in a CNS cell of said subject.